Supplementary Appendix

Supplement to: Lin D-Y, Xu Y, Gu Y, et al. Effectiveness of bivalent boosters against severe omicron infection. N Engl J Med. DOI: 10.1056/NEJMc2215471

This appendix has been provided by the authors to give readers additional information about the work.

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Supplemental Methods

Study Design

We obtained individual-level data on vaccination histories from December 11, 2020 to December 8, 2022 and on clinical outcomes (SARS-CoV-2 infection, hospitalization, and death) from March 11, 2020 to December 8, 2022 by linking the North Carolina COVID-19 Surveillance System and COVID-19 Vaccine Management System through a Master Patient Index. These data sources have been described elsewhere.[1-3] The previous studies used vaccination and outcome data collected through June 3, 2022, whereas this study focused on the vaccination and outcome data collected from May 25 to December 8, 2022.

We considered two study periods of 99 days during which the omicron variant was predominant in the United States. Figure S1 shows the proprotions of circulating strains over the course of the study. In the first period, from May 25 to August 31, 2022, monovalent mRNA vaccines were administered as boosters. In the second period, from September 1 to December 8, 2022, bivalent mRNA vaccines were administered as boosters to individuals who had previously reveived monovalent or non-mRNA vaccines. Ideally, we would have liked to compare bivalent and monovalent boosters administered during the same time period. However, monovalent vaccines were replaced by bivalent vaccines as booster doses for all individuals 12 years of age and older in the U.S. beginning on September 1, 2022. Thus, we chose the 99-day period of monovalent boosters that was the closest to the 99-day period of bivalent boosters. This design shares the spirit of the discontinuity design for causal inference.

For each study period, we identified all individuals 12 years of age and older who had completed a primary vaccine series, had received a first booster dose, or had received a second booster dose before the start of the study period. We excluded children less than 12 years old because bivalent boosters were not extended to ages 5-11 years until October 12, 2022. The main exposure was the new booster dose, which was the first, second, or third booster dose for individuals who had received only the primary series, only the first booster dose, or two booster doses, respectively, and the outcomes were the new cases of omicron infection, hospitalization, and death. We focused on severe infection resulting in hospitalization or death.

COVID-19 case data were populated according to lab reports from clinical laboratories that are mandated to report results. At-home testing results were not included. Our dataset contained positive COVID-19 test results for all cases and index reinfections using the unique person identifier and person-event infection variables. COVID-19-related hospitalization and death were documented through local health department case investigation. For cases reported on January 1, 2022 and going forward, vital records criteria were introduced to expand COVID-19 death surveillance. The definitions of COVID-19 cases and deaths can be found at https://covid19.ncdhhs.gov/dashboard/cases-and-deaths#covid-19-cases-and-deaths.

An increasing number of individuals have taken home-based testing, which is not reported to local health departments. When disease severity increases, those individuals may be admitted to the hospital, where a Covid-19 test is administered for diagnostic purposes. In these situations, the time of Covid-19 diagnosis would be equal to or greater than the time of hospitalization. In the monovalent booster period of our study, 13,560 Covid-19 cases were diagnosed on the day of hospitalization, and 2,328 were diagnosed after the day of hospitalization. In the bivalent booster period of our study, 14,444 Covid-19 cases were diagnosed on the day of hospitalization, and 2,490 were diagnosed after the day of hospitalization. If Covid-19 diagnosis occurred after hospitalization, then the date of infection was set to the date of hospitalization in our analysis.

We used the genetic sequence-based surveillance data produced by the Centers for Disease Control and Prevention (https://covid.cdc.gov/covid-data-tracker/#variant-proportions) to determine the circulating variants and strains and generated Figure S1. No individual-level sequence data were available.

Statistical Analysis Plan

For each study period and each outcome, we fit the Cox regression model in which the log hazard ratio for a booster dose is a continuous B-spline function of the time elapsed since receipt of a booster dose.[1-3] To ascertain the ramping and waning patterns, we use a piecewise linear function with change points at 2 and 4 weeks (i.e., 14 and 28 days) after receipt of a booster dose. To estimate an average booster effect over days 15–99 after receipt of a booster dose, we set the log hazard ratio to be linear between day 0 and day 14 and be constant after day 14. (The latter model involves only a single unknown regression parameter, which can be estimated with higher accuracy than the multiple unknown regression parameters in the first model.) To reduce confounding bias due to time trends in disease incidence, we measure the event time for each person from the start of the study period, such that the risks of disease for boosted and non-boosted persons are compared on the same calendar date. To further reduce confounding bias, we include vaccine manufacturer and date of previous vaccination (and the product between these two variables), time since most recent infection (which is set to 0 if the individual was not previously infected), and demographic factors (i.e., sex, age group, race/ethnicity, geographic region, and county-level vaccination rate) as covariates. We also include the vaccination status at the start of the study period (receipt of only the primary vaccine series, receipt of only the first booster dose, or receipt of two booster doses) as two indicator covariates, allowing individuals with different baseline vaccination statuses to have different disease risks.

We consider two clinical endpoints. The first one is time to severe infection resulting in hospitalization. Death is treated as a competing risk for hospitalization, such that the analysis pertains to the cumulative incidence of hospitalization. The second endpoint is time to severe infection resulting in hospitalization or death, whichever occurs first. Analyses are planned for

certain subgroups, including age groups, mRNA primary vaccine receipients, Moderna versus Pfizer-BioNTech boosters, booster number, and prior infection status.

The effect of a new booster dose is characterized by the hazard ratio (HR) in the above Cox regression model. The vaccine effectiveness (VE) is defined to be 100x(1–HR)%. Maximum partial likelihood is used to estimate HR and VE, and 95% confidence intervals are constructed. The confidence interval for the difference between the bivalent and monovalent booster effectiveness is constructed by the bootstrap method with 300 bootstrap samples. The estimation results for the first model are shown in Figures S2, and those of the second model are shown in Figure S3 and Table 1.

References

1. Lin DY, Gu Y, Wheeler B, et al. Effectiveness of Covid-19 vaccines over a 9-month period in North Carolina. N Engl J Med 2022; 386: 933-941.
2. Lin DY, Gu Y, Xu Y, et al. Association of primary and booster vaccination and prior infection with SARS-CoV-2 infection and severe COVID-19 outcomes. JAMA 2022; 328: 1415-1426.
3. Lin DY, Gu Y, Xu Y, et al. Effects of vaccination and previous infection on omicron infections in children. N Engl J Med 2022; 387: 1141-1143.

Table S1. Demographic and Clinical Characteristics of Study Participants.

Baseline Characteristic	Monovalent Booster Period					Bivalent Booster Period				
	No. of Persons	No. of Boosters[a]	No. of Clinical Outcomes			No. of Persons	No. of Boosters[a]	No. of Clinical Outcomes		
			Infections	Hosp	Death			Infections	Hosp	Death
Total	6,242,259	292,659	201,589	1,896	690	6,283,483	1,070,136	76,636	1,093	514
Vaccination status										
Primary series	3,068,644	125,704	85,984	818	289	2,981,689	182,455	31,209	440	198
First booster	2,945,565	166,796	108,649	983	366	2,906,967	681,586	39,473	551	251
Second booster	228,050	159	6,956	95	35	394,827	206,095	5,954	102	65
Prior Infection										
Yes	1,116,561	49,392	28,221	194	193	1,301,095	166,390	14,123	164	238
No	5,125,698	243,267	173,368	1,702	497	4,982,388	903,746	62,513	929	276
Sex										
Female	3,406,828	169,501	123,153	954	336	3,429,689	606,608	48,009	553	255
Male	2,835,431	123,158	78,436	942	354	2,853,794	463,528	28,627	540	259
Age group										
12-17	330,287	18,273	5,725	7	0	346,209	32,678	3,308	7	1
18-34	1,324,203	27,917	44,492	66	5	1,338,406	101,439	14,276	18	1
35-49	1,314,806	28,695	46,892	101	13	1,320,863	159,390	15,180	46	8
50-64	1,533,695	87,574	53,290	316	77	1,537,100	268,251	19,990	185	52
⩾65	1,739,268	130,200	51,190	1,406	595	1,740,905	508,378	23,882	837	452
Race/Ethnicity										
Black or Hispanic	1,816,673	87,233	65,029	480	145	1,835,084	211,501	23,194	258	110
Other	4,425,586	205,426	136,560	1,416	545	4,448,399	858,635	53,442	835	404
Geographic Region										
Coastal	1,518,459	73,014	51,305	529	188	1,529,261	212,912	18,141	265	149
Piedmont	4,049,542	182,472	132,531	1,204	417	4,076,562	721,794	50,089	749	296
Mountain	674,258	37,173	17,753	163	85	677,660	135,430	8,406	79	69
County Vaccination										
<62%	1,659,006	75,530	55,338	800	252	1,671,075	214,566	22,462	422	177
62-75%	2,021,830	98,737	63,155	705	250	2,035,035	330,649	25,932	419	201
>75%	2,561,423	118,392	83,096	391	188	2,577,373	524,921	28,242	252	136

a. Boosters pertain to first, second, and third boosters for participants with primary, first booster, and second booster vaccination, respectively, at baseline.

Table S2. Numbers of Hospitalization and Death for the Booster and Non-Booster Groups.

	Monovalent Booster Period			Bivalent Booster Period		
	No. of Persons	No. of Hosp.[a]	No. of Death[a]	No. of Persons	No. of Hosp.[a]	No. of Death[a]
All Persons						
Non-booster	5,949,600	1,807	667	5,213,347	954	497
Booster	292,659	61	23	1,070,136	57	17
Age ⩾18 yrs						
Non-booster	5,637,586	1,801	667	4,899,816	948	496
Booster	274,386	61	23	1,037,458	57	17
Age ⩾65 yrs						
Non-booster	1,609,068	1,336	573	1,232,527	717	437
Booster	130,200	55	22	508,378	53	14
mRNA Primary Vaccine						
Non-booster	5,521,112	1,721	632	4,807,141	909	476
Booster	280,228	56	21	1,033,295	56	17
Pfizer-BioNTech Product						
Non-booster	5,949,600	1,807	667	5,213,347	954	497
Booster	164,693	31	11	659,422	36	11
Moderna Product						
Non-booster	5,949,600	1,807	667	5,213,347	954	497
Booster	127,966	30	12	410,714	21	6
First Booster						
Non-booster	2,942,940	783	279	2,799,234	408	196
Booster	125,704	22	9	182,455	7	2
Second Booster						
Non-booster	2,778,769	925	353	2,225,381	470	239
Booster	166,796	39	14	681,586	36	12
Third Booster						
Non-booster	227,891	99	35	188,732	76	62
Booster	159	0	0	206,095	14	3
Previously Infected						
Non-booster	1,067,169	185	145	1,134,705	120	189
Booster	49,392	5	4	166,390	10	5
Previously Uninfected						
Non-booster	4,882,431	1,622	522	4,078,642	834	308
Booster	243,267	56	19	903,746	47	12

a. In the booster group, hospitalizations and deaths that occurred before receipt of booster are excluded.

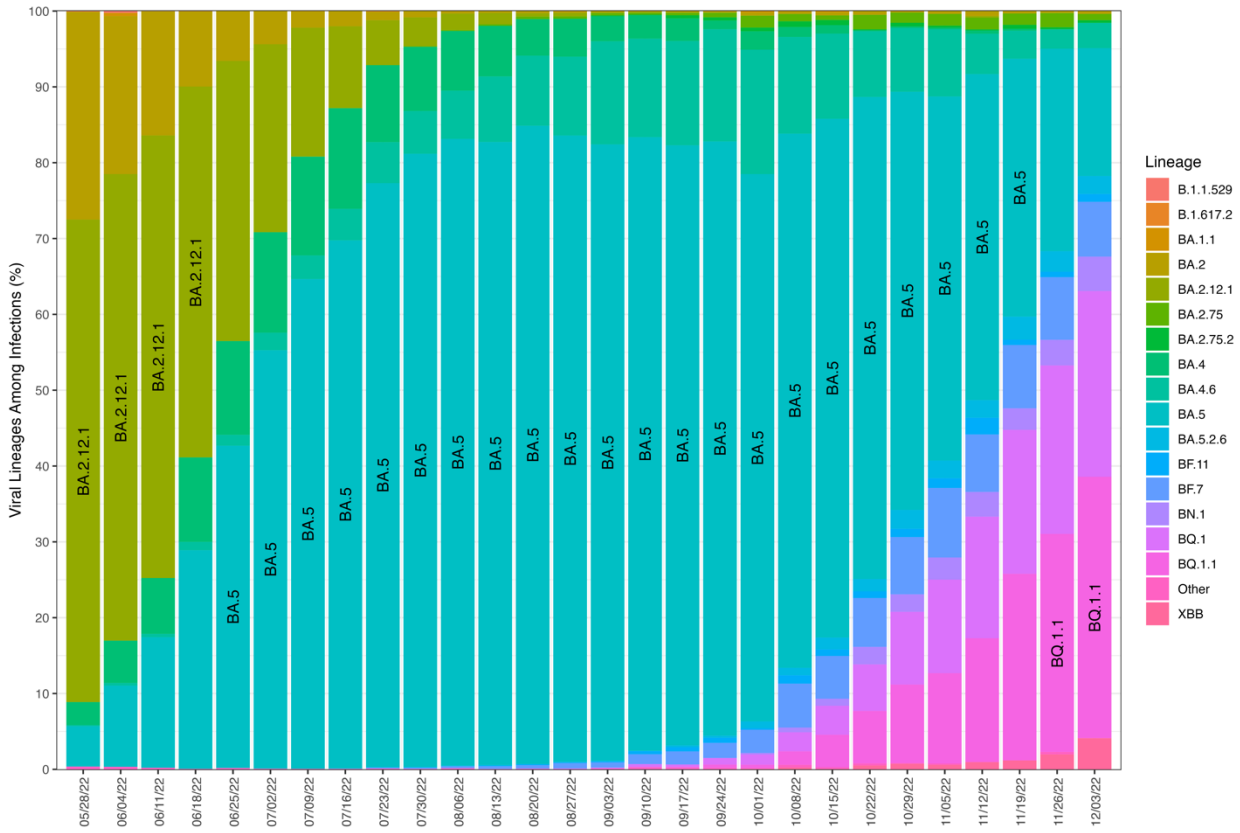

Figure S1. Variant Proportions in the State of North Carolina During the Study. The dominant variant is labelled on each bar.

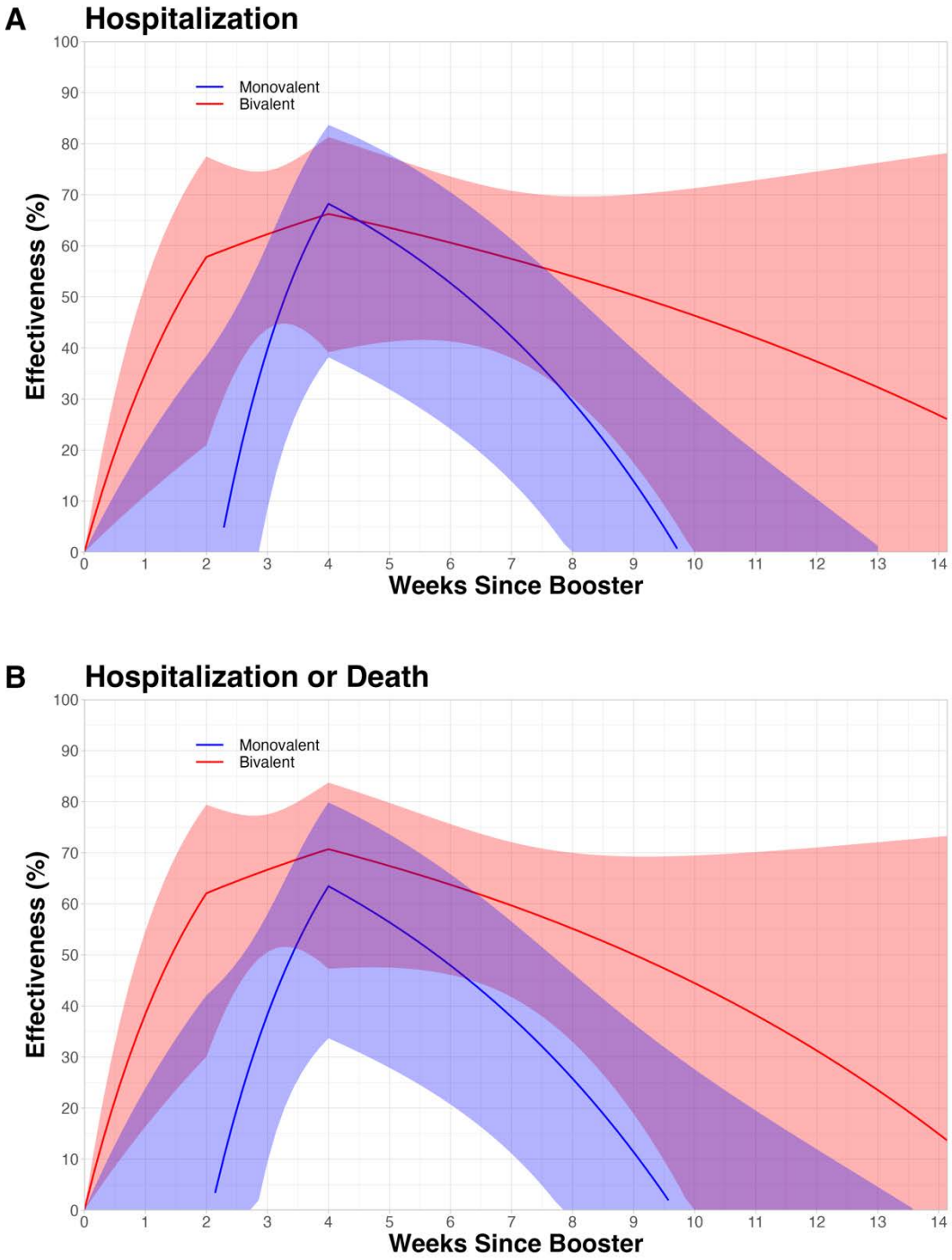

Figure S2. Effectiveness of One Monovalent or Bivalent Booster Dose Against Severe Omicron Infection Over Time for All Participants. The log hazard ratio for a booster dose is approximated by a continuous, piecewise linear function with change points at 2 and 4 weeks after receipt of booster. The solid curves show the estimates of booster effectiveness. The shaded bands indicate 95% confidence intervals**.**

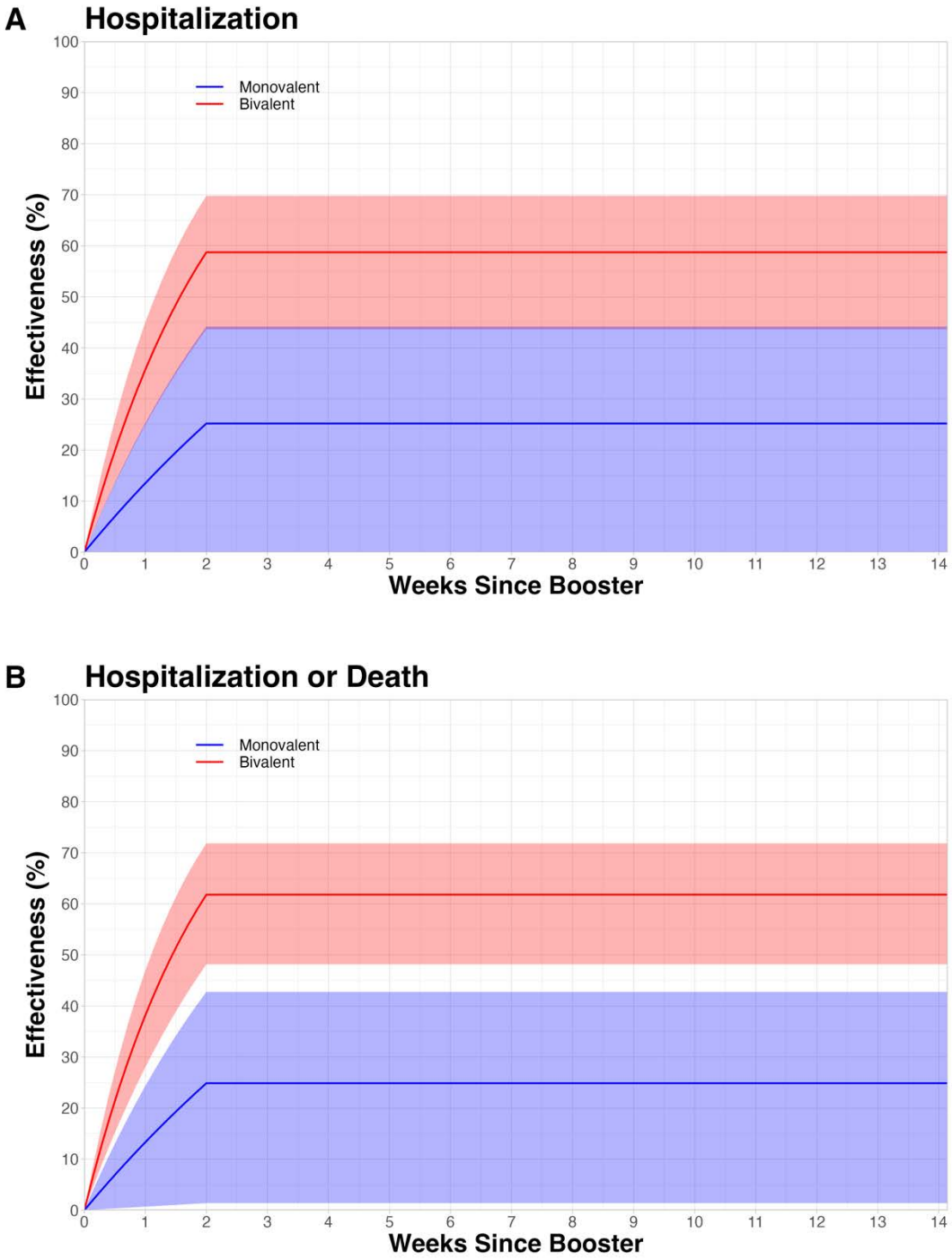

Figure S3. Average Effectiveness of One Monovalent or Bivalent Booster Dose Against Severe Omicron Infection for All Participants. The log hazard ratio for a booster dose is assumed to be linear between days 0 and 14 after receipt of booster and be constant after day 14. The solid curves show the estimates of booster effectiveness. The shaded bands indicate 95% confidence intervals.